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Published in:
European Neuropsychopharmacology

DOI:
10.1016/j.euroneuro.2006.09.003

Publication date:
2007

European Neuropsychopharmacology (2007) **17**, 309–311

www.elsevier.com/locate/euroneuro

SHORT COMMUNICATION

Non-steroidal anti-inflammatory drugs and the risk of psychosis

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Received 27 June 2006; received in revised form 5 September 2006; accepted 22 September 2006

KEYWORDS
Schizophrenia;
Psychosis;
NSAID;
Inflammation

Abstract The objective of the current research was to examine the relation between non-steroidal anti-inflammatory drugs (NSAID) use and risk of psychosis. To this end we performed a longitudinal case-control study using prescription data from a Dutch health insurance company. Men aged 25 years or over and women aged 30 years or over were excluded to prevent inclusion of non-incident cases. This resulted in eighty-two cases and 359 randomly selected controls from the same population. The overall relative risk of incident antipsychotic use for NSAID users, adjusted for age and prescription frequency, was 0.80 (95% CI: 0.48–1.33). After stratification for gender the risk of psychosis was significantly lower (59%) in male NSAID users only. The relative risks for male and female subjects were 0.41 (95% CI: 0.17–0.97) and 1.31 (95% CI: 0.65–2.64), respectively. These results suggest that in men NSAIDs may lower the risk of psychosis.

1. Introduction

A negative association between the occurrence of rheumatoid arthritis and schizophrenia has been known for a long time (Mors et al., 1999). This suggests involvement of the immune system in the pathophysiology of schizophrenia. Indeed, immune alterations have been observed in patients with schizophrenia (Cazzullo et al., 2001; Korschenhausen et al., 1996; Maes et al., 1995; Naudin et al., 1997; Schwarz et al., 2001), although it cannot be excluded that these changes result from long-term neuroleptic treatment (DeLisi, 1996). Some of the immunological changes may be counteracted by prostaglandin inhibitors, e.g. non-steroidal anti-inflammatory drugs (NSAIDs). Muller et al. (2002) showed a beneficial effect of add-on therapy with celecoxib. Improved understanding of the putative relation between NSAID use and risk of psychosis may shed a light on the immunological inflammation hypothesis and may point at new treatment options.

The present study aims to longitudinally investigate the relation between NSAID use and subsequent schizophrenic

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doi:10.1016/j.euroneuro.2006.09.003

Table 1 Relative risk of psychosis according to NSAID use (with 95% confidence interval), for the group as a whole and for men and women separately

	Unadjusted	Adjusted for age	Adjusted for age and prescription frequency
Men	0.58 (0.26–1.31)	0.44 (0.19–1.05)	0.41 (0.17–0.97)
Women	1.47 (0.78–2.90)	1.47 (0.74–2.90)	1.31 (0.65–2.64)
Total	0.87 (0.53–1.42)	0.85 (0.51–1.40)	0.80 (0.48–1.33)

psychosis. The relation was additionally studied in men and women separately because males are at a considerably higher psychosis risk than females (Aleman et al., 2003), and because the negative association with rheumatoid arthritis has shown to be modified by gender (Mors et al., 1999).

2. Experimental procedures

We performed a prospective nested case-control analysis using anonymized pharmacy records from the Agis Health Insurance Database (N=550,000). Data on all prescribed NSAIDs (ATC-codes N02BA (01-to-79) and M01A (A01-to-X68) and anti-psychotics (ATC-code N05A (A01-to-X12) between 1995 and 2002 were extracted.

All study subjects were registered at the insurance company for at least 5 years. Cases were those insured with first use of anti-psychotics during at least 3 months in the years 2000 to 2002. To prevent inclusion of non-incident cases, men aged 25 years or over and women aged 30 years or over were excluded. These age cut-offs correspond to the respective mean ages of disease onset (Hafner, 2003). Controls were a random, four times larger sample of non-cases from the same database. We took account of prescription frequency of any medication because cases who were socially withdrawing before disease onset may have been less likely to visit a general practitioner and consequently, to receive any medication, including an NSAID.

For cases, NSAID use and prescription frequency were defined as any prescription for NSAIDs and total number of prescriptions per year in the 4 years preceding anti-psychotics use. For controls this period was defined by calendar years 1999 to 2002. Subjects using lithium suggesting bipolar disorder, or methotrexate or sulfasalazine suggesting rheumatoid arthritis, were excluded. We calculated odds ratios (OR) with 95% confidence intervals (95% CI) as measures of relative risk of NSAID use for psychosis.

Using logistic regression additional adjustments were made for age and prescription frequency. We repeated the analyses while stratifying for gender.

3. Results

Eighty-two cases and 359 controls were included in the analysis. Cases showed the same mean age as controls (21 years) but a higher proportion of males (52 versus 30%) and a higher mean prescription frequency (6.5 versus 4.8/year). The four-year cumulative incidence of NSAID use in the source population, as estimated from the controls, was 41% (95% CI 36–46%). Among NSAID users mean age was 22 years (range 13 to 30) and 26% was male. For non-NSAID users mean age was 20 years (range 12 to 30) and 40% was male. Mean age for males was 19 years and 22 years for females.

Overall, the relative risk of psychosis for NSAID users was 0.87 (95% CI: 0.53–1.42). After adjustment for age and prescription frequency the relative risk was similar, i.e. 0.80 (95% CI: 0.48–1.33). Further analyses were stratified for gender (Table 1). NSAID use was significantly related to a 59% decreased risk of psychosis in men (adjusted relative risk 0.41 (95% CI: 0.17–0.97)) while in women, NSAID use was associated with a small and statistically non-significant increase in risk (1.31 (95% CI: 0.65–2.64)). The two-tailed p-value for interaction between gender and NSAID use was 0.08.

4. Discussion

The results of the present study show a protective effect of NSAIDs on the risk for treated psychosis in men only.

To appreciate this finding, some characteristics of the study need to be addressed. The incident use of anti-psychotics was used in this analysis as a proxy for incident psychosis. In both a Dutch and an Italian study (Barbui et al., 2004; Rijcken et al., 2003) a substantial part of anti-psychotics were prescribed for other indications, notably non-schizophrenic psychosis. This could have resulted in a slight overestimation of the true incidence of schizophrenic psychosis. As it is highly unlikely that this overestimation has selectively affected NSAID users, the consequent misclassification has been non-differential, with underestimation of the observed effect as a result. Another potential limitation of the data is that prescription data may not completely cover NSAID use in the population. In the Netherlands certain NSAIDs can be without prescription, i.e. over the counter. Consequently insurance companies will not register these NSAIDs, leading to an underestimation of true NSAID use. If subjects in the prodromal phase of psychosis were more likely to omit a visit to their general practitioner than healthy subjects and consequently perhaps used more over the counter NSAIDS instead, overestimation of the protective effect may have occurred. To antagonize this potential bias we controlled in the analyses for prescription frequency for any medication. Yet, overall prescription frequency may not fully capture the tendency of cases to visit their GP.

Our findings agree with previous reports from the limited number of studies carried out in this area. In a case report review by Jiang and Chang (1999) 5 cases with adverse psychiatric reactions to NSAIDs are described. This suggests that the use of NSAIDs at least may have an effect on the central nervous system. As far as we know only one study addressed the effect of NSAIDS on psychosis directly. In this study, a randomized trial by Muller (Muller et al., 2002) 25 male and 25 female patients with acute exacerbation of schizophrenia were randomly assigned to either risperidone plus celecoxib (COX-2 NSAID), or risperidone plus placebo. The celecoxib group showed significantly greater improvement in total PANSS (Positive and Negative Syndrome Scale) scores indicating that the addition of NSAIDs to regular anti-psychotic treatment may have beneficial effects on the

course of schizophrenia. Unfortunately, no gender-specific results were presented.

A possible effect of NSAIDs on the occurrence and course of psychosis is plausible in view of a number of mechanisms proposed in the literature.

Psychotic symptoms have been described in processes accompanied by a process of inflammation and in several autoimmune disorders involving the CNS (Chong et al., 2003; Hanson and Gottesman, 2005; Muller et al., 2004). Signs of inflammation were found in the post-mortem CNS tissues of some schizophrenic patients (Korschenhausen et al., 1996) Recently, it has been discovered that the *cyclo*-oxygenase enzyme in platelets, which is inhibited by NSAIDs, is hyperactive in schizophrenia (Das and Khan, 1998). The observations of our study suggest that the use of NSAIDs might reduce the risk of schizophrenia in males only. An explanation for the absence of a positive effect of NSAIDS in women may be that the supposed protection by estrogens (Riecher-Rössler, 2002) leaves little room for positive effects of NSAIDs.

In conclusion, our findings in a large cohort study with over 80 patients with incident treated psychosis support the view that NSAIDs may reduce the risk of future psychosis, although this effect appears to be restricted to males.

Acknowledgements

The Health Insurance Company Agis, Amersfoort, the Netherlands, is greatly acknowledged for supplying the data. This research was supported by the Stanley Medical Research Institute.

References

Aleman, A., Kahn, R.S., Selten, J.P., 2003. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Archives of General Psychiatry 60 (6), 565–571.

Barbui, C., Ciuna, A., Nose, M., Patten, S.B., Stegagno, M., Burti, L., Amaddeo, F., Tansella, M., 2004. Off-label and non-classical prescriptions of antipsychotic agents in ordinary in-patient practice. Acta Psychiatrica Scandinavica 109 (4), 275–278.

Cazzullo, C.L., Sacchetti, E., Galluzzo, A., Panariello, A., Colombo, F., Zagliani, A., Clerici, M., 2001. Cytokine profiles in drug-naive schizophrenic patients. Schizophrenia Research 47 (2–3), 293–298.

Chong, J.Y., Rowland, L.P., Utiger, R.D., 2003. Hashimoto Encephalopathy: syndrome or myth? Archives of Neurology 60 (2), 164–171.

Das, I., Khan, N.S., 1998. Increased arachidonic acid induced platelet chemiluminescence indicates cyclooxygenase overactivity in schizophrenic subjects. Prostaglandins, Leukotrienes and Essential Fatty Acids 58 (3), 165–168.

DeLisi, L.E., 1996. Is there a viral or immune dysfunction etiology to schizophrenia? Re-evaluation a decade later. Schizophrenia Research 22 (1), 1–4.

Hafner, H., 2003. Gender differences in schizophrenia. Psychoneuroendocrinology 28 (Supplement 2), 17–54.

Hanson, D.R., Gottesman, I.I., 2005. Theories of schizophrenia: a genetic-inflammatory-vascular synthesis. BMC Medical Genetics 6, 7.

Jiang, H.K., Chang, D.M., 1999. Non-steroidal anti-inflammatory drugs with adverse psychiatric reactions: five case reports. Clinical Rheumatology 18 (4), 339–345.

Korschenhausen, D.A., Hampel, H.J., Ackenheil, M., Penning, R., Muller, N., 1996. Fibrin degradation products in post mortem brain tissue of schizophrenics: a possible marker for underlying inflammatory processes. Schizophrenia Research 19 (2–3), 103–109.

Maes, M., Bosmans, E., Calabrese, J., Smith, R., Meltzer, H.Y., 1995. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. Journal of Psychiatric Research 29 (2), 141–152.

Mors, O., Mortensen, P.B., Ewald, H., 1999. A population-based register study of the association between schizophrenia and rheumatoid arthritis. Schizophrenia Research 40 (1), 67–74.

Muller, N., Riedel, M., Scheppach, C., Brandstatter, B., Sokullu, S., Krampe, K., Ulmschneider, M., Engel, R.R., Moller, H.J., Schwarz, M.J., 2002. Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. American Journal of Psychiatry 159 (6), 1029–1034.

Muller, N., Ulmschneider, M., Scheppach, C., Schwarz, M.J., Ackenheil, M., Moller, H.J., Gruber, R., Riedel, M., 2004. COX-2 inhibition as a treatment approach in schizophrenia: immunological considerations and clinical effects of celecoxib add-on therapy. European Archives of Psychiatry and Clinical Neuroscience 254 (1), 14–22.

Naudin, J., Capo, C., Giusano, B., Mege, J.L., Azorin, J.M., 1997. A differential role for interleukin-6 and tumor necrosis factor-[alpha] in schizophrenia? Schizophrenia Research 26 (2–3), 227–233.

Riecher-Rössler, 2002. Oestrogen effects in schizophrenia and their potential therapeutic implications — review. Archives of Women's Mental Health 5 (3), 111–118.

Rijcken, C.A., Boelema, G.J., Slooff, C.J., Beuger, P.J., Tanja, T.A., de Jong-van den Berg, L.T., 2003. Off-label use of antipsychotics in the community pharmacy: the sex differences. Pharmacopsychiatry 36 (5), 187–191.

Schwarz, M.J., Chiang, S., Muller, N., Ackenheil, M., 2001. T-helper-1 and T-helper-2 responses in psychiatric disorders. Brain, Behavior, and Immunity 15 (4), 340–370.